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Submitted via Email: esther.barajas-ochoa@oehha.ca.gov

**RE: COMMENTS ON PROPOSED NO SIGNIFICANT RISK LEVEL FOR
GLYPHOSATE**

Dear Ms. Barajas-Ochoa:

Date June 21, 2017

We are submitting the following comments on behalf of The Scotts Company LLC (Scotts) in response to the Office of Environmental Health Hazard Assessment's (OEHHA) proposed No Significant Risk Level (NSRL) for glyphosate.

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In developing an NSRL for glyphosate, OEHHA has focused on the incidence of hemangiosarcomas reported in male CD-1 mice following administration of 0, 100, 300, or 1000 mg glyphosate/kg/day in the mice's diet for two years. As noted in the documentation of the NSRL (OEHHA 2017), this is an unpublished study conducted by Inveresk Research International (Atkinson et al. 1993), with summaries of the study provided in the 2006 Joint FAO/WHO Meeting on Pesticide Residues report (JMPR 2006) and a monograph from the International Agency for Research on Cancer (IARC 2015). The incidence of hemangiosarcomas reported in the male CD-1 mice is 0/50, 0/50, 0/50 and 4/50 following administration of 0, 100, 300, or 1000 mg/kg/day, respectively. OEHHA (2017) and IARC (2015) both rely upon the summary of the report provided by JMPR (2006). However, both OEHHA and IARC failed to consider additional conclusions from JMPR (2006) in interpreting the significance of this endpoint, and thus improperly reached conclusions regarding use of this dataset in estimating the potential carcinogenicity of glyphosate in humans. JMPR (2006) reports that,

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"Owing to the lack of a dose-response relationship, the lack of statistical significance and the fact that the incidences recorded in this study fell within the historical ranges for controls, these changes are not considered to be caused by administration of glyphosate."

In conclusion, administration of glyphosate to CD-1 mice for 104 weeks produced no signs of carcinogenic potential at any dose. The NOAEL was 1000 mg/kg bw per day, the highest dose tested (Atkinson et al. 1993)."

The observed tumors in the high dose group are also within the range of historical control incidence for this type of tumor (2-12%) (Williams et al. 2016). Therefore, these conclusions would indicate that while a significant trend may have been observed, there are reasons why the observed incidence in the male CD-1 mice reported in the Atkinson et al. (1993) study is not related to treatment with glyphosate. In the female mice of the same study, no dose-related incidence of hemangiosarcoma was reported (0/50, 2/50, 0/50, 1/50). In addition, in a separate study conducted in CD-1 mice at comparable concentrations (up to 946 mg/kg/day) for 18 months (Nufarm 2009 – as cited in Greim et al. 2015; Williams et al. 2016), no statistically significant increases in any tumor type were reported. This would suggest that the overall evidence for this tumor type does not establish consistency across studies that is needed to provide a causal connection between exposure to glyphosate and cancer. Therefore, the reliance upon this dataset to predict the potential for carcinogenicity in humans could be considered the use of a "negative" dataset, or reliance on incidence of a tumor type that is not related to exposure to glyphosate. The use of this type of data results in high uncertainty and should not be relied upon for quantitative estimation of an NSRL.

Moreover, the incidence above zero of hemangiosarcoma in the male rat relied upon for the NSRL occurred only at the highest concentration tested (1000 mg/kg/day). The dataset selected for the derivation of a value, such as an NSRL, should show clear evidence of a dose-response and statistically significant differences in incidence in the treated groups versus controls. Conducting dose-response modeling with a limited dataset – such as the dataset used in the derivation of the NSRL for glyphosate, which provides the observation of incidence above zero only at the highest concentration – creates significant model uncertainty. This type of dataset lacks the necessary information to inform the shape of the dose-response curve in the low concentration region, which is needed for extrapolation to concentrations relevant to the human population and thus to estimate an NSRL. The lack of a statistically-significant increase in the incidence in the high concentration group compared to the incidence in concurrent controls, combined with lack of incidence in the low concentration region, introduces significant uncertainty in estimating the potential for health effects at low concentrations (if any exist) that would be associated with a 1×10^{-5} risk level (the risk level associated with the NSRL).

Other datasets which have a positive trend or pair-wise significance have been evaluated by many committees and authoritative bodies for causal associations with glyphosate exposure (JMPR 2006; Williams et al. 2016; Greim et al. 2015; USEPA 2016) and provide no alternative datasets that would be appropriate for estimating an NSRL. For these datasets, multiple reviewers have noted the need to consider the dose-response pattern, historical control information, and progression to malignancy in drawing conclusions regarding the potential carcinogenicity of glyphosate based on the available animal studies. These considerations are also relevant in selecting a dataset upon which to base a quantitative estimate of the potential health risk or an acceptable level of exposure, such as an NSRL. All of the remaining datasets indicate incidences that are within the historical control range, are benign responses, or are present only at very high doses with no significant increase in incidence at lower concentrations, and thus should not be relied upon for quantitative estimates of potential cancer risk in humans. The lack of an adequate dataset

for estimating an NSRL is consistent with conclusions reached by JMPR (2006) and USEPA (2016) that any tumor findings observed in the available rat and mouse carcinogenicity studies are not treatment-related, thus providing no evidence that glyphosate is carcinogenic. It is also consistent with the opinion for glyphosate from the Committee for Risk Assessment of the European Chemicals Agency (ECHA 2017) that “based on the epidemiological data as well as the data from long-term studies in rats and mice, taking a weight of evidence approach, no classification for carcinogenicity is warranted.”

In weighing the available evidence for a dose-response assessment, as with a hazard characterization, consideration of not only the likelihood of human carcinogenic effects of the agent but also the conditions under which such effects may be expressed is necessary. In the case of glyphosate, there are no datasets from the animal studies that provide evidence of a strong dose-response relationship of carcinogenicity following glyphosate exposure that could be relied upon to estimate the potential for carcinogenic health effects in humans following exposure to concentrations expected in the human population.

Yours sincerely



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